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Inside this issue

1 Environmental factors associated with autism spectrum disorder: a scoping review for the years 2003–2013

24 Status report – The Public Health and Planning 101 project: strengthening collaborations between the public health and planning professions

30 At-a-glance – Emergency department surveillance of thermal burns and scalds, electronic Canadian Hospitals Injury Reporting and Prevention Program, 2013

32 Letter to the Editor – Who benefits from the professionalization of health promotion?

33 Other PHAC publications

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Canada

Environmental factors associated with autism spectrum disorder: a scoping review for the years 2003–2013

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Abstract

Introduction: The number of children diagnosed with autism spectrum disorder (ASD) has been rapidly rising in the past decade. The etiology of this disorder, however, is largely unknown, although the environmental relative to the genetic contribution is substantial. We conducted a scoping review to comprehensively assess the current state of knowledge of the environmental factors present from preconception to early life associated with ASD, and to identify research gaps.

Methods: We searched electronic databases MEDLINE, PsycINFO and ERIC for articles on potential risk factors or protective factors from the physical and social environments associated with ASD and its subclassifications published between 1 January, 2003, and 12 July, 2013. We categorized articles into broad themes: chemical, physiological, nutritional and social factors, based on environmental exposure.

Results: We identified over 50 000 publications, but after ineligible studies were screened out, 315 articles remained. Most of these studies examined physiological factors, followed closely by chemical factors, and to a much lesser extent, nutritional and social factors, associated with ASD. Despite a vast literature and many heterogeneous studies, several risk factors emerged consistently: chemical factors such as traffic-related air pollutants; physiological factors including advanced parental age, preterm birth, low birth weight, hyperbilirubinemia and clustering of pregnancy complications; and maternal immigrant status. Despite extensive research on vaccines, findings overwhelmingly demonstrate no support for an association with ASD.

Conclusion: The lack of consistency, temporality and specificity of associations between environmental factors and ASD remains the largest barrier to establishing causal relationships. More robust research is required to resolve inconsistencies in the literature. Future research should explore underlying mechanisms of associations between the risk factors that we identified and ASD.

Keywords: ASD, autism spectrum disorder, autism, environmental exposure, etiology

Highlights

- The environmental factors most commonly studied in association with ASD were physiological and chemical factors. Research on nutritional and social factors is limited.
- Older parental age, low birth weight, premature birth, neonatal jaundice and clustering of pregnancy complications were consistently reported to be associated with ASD.
- Evidence for the association between traffic-related air pollutants and ASD has been emerging.
- Maternal immigrant status was consistently associated with ASD.
- The lack of consistency, temporality and specificity of associations between environmental factors and ASD remains the largest barrier to establishing causal relationships.

Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders with varying levels of severity in impairment in social communication and interaction, and restricted repetitive behaviours, interests and activities.[1] The number of children with ASD has been rapidly rising in the past decade.[2] In the US, the number of cases increased by 123% from 2002 to 2010, with an estimated prevalence of 1 in 68 children aged 8 years.[3] In Canada, from 2003 to 2010, increases of 70% and 95% were reported in Prince Edward Island and Southeastern Ontario, respectively, with corresponding prevalence of 1 in 106 and 1 in 63 children aged 6 to 9 years in 2010.[4] Greater ASD awareness and changes in diagnostic criteria may be contributing factors,[5] but explain only a portion of the increased prevalence.[6,7] Although the genetic contribution to the etiology of ASD is known,[8] the rapid increase in ASD prevalence cannot be fully attributed to genetics alone.

A twin concordance study has shown that shared environmental factors account for 58% of the variance in liability for ASD.[8] Furthermore, prenatal and early infancy periods are known to be critical periods of growth during which children are particularly vulnerable to harmful effects of environmental hazards that can result in childhood diseases.[9] However, the role of environmental factors in the onset of ASD is still largely unknown. Of the reviews that have explored possible risk factors of ASD to date,[10-16] none have comprehensively examined the entire scope of the environmental contribution to ASD.

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The purpose of this scoping review is to comprehensively assess the current state of knowledge of environmental factors associated with ASD incidence and to identify research gaps. Specifically, we aim to identify any environmental exposures, including chemical, physiological, nutritional and social factors, from preconception to early-life periods associated with ASD.

Methods

This review followed Arksey and O'Malley's scoping framework.[17] We searched the electronic databases MEDLINE, PsycINFO and ERIC for primary studies or reviews on potential modifiable risk factors or protective factors from the physical or social environment associated with ASD. We developed a comprehensive list of medical subject headings and keywords with the help of a librarian at the University of Ottawa. Search terms were centred on two main concepts: (1) ASD and its subclassifications, including pervasive development disorder not otherwise specified (PDD-NOS), autism and Asperger syndrome; and (2) environmental exposures or risk factors, maternal condition before or during pregnancy, and paternal preconception condition. The search strategy was adapted appropriately to the other databases, PsycINFO and ERIC, using their corresponding subject heading terms. Searches were limited to articles with an abstract published in the English language with a publication date between 1 January, 2003, and 12 July, 2013, to focus on current literature. We excluded articles if the epidemiological associations they described included comorbidities, the result of living with ASD or biochemical pathways not directly related to etiology; we also excluded studies that used animal models, cell studies and strictly genetic studies. Commentaries, editorials, letters, news articles and articles that did not primarily focus on ASD etiology were also filtered out.

We categorized journal articles into broad themes: chemical, physiological, nutritional, social and other, based on the nature of the environmental exposure examined. Within each broad theme, we identified recurring subthemes. We abstracted publication year, study design, study population, exposure, confounders, case definition and main findings from each full-text article. The review process resulted in 315 articles for final analysis (Figure 1). Our review focussed mainly on primary studies and systematic reviews.

Results

The literature encompassed a wide scope of research investigating potential environmental risk factors associated with ASD. Research has been conducted worldwide; many studies were concentrated in the Nordic countries, the United States, the United Kingdom, Australia and Japan. Most studies examined physiological factors, followed closely by chemical factors, and then nutritional and social factors associated with ASD (Table 1; Figure 2). There was some overlap between these areas as several studies examined a combination of factors; about 14% of the articles (44/315) explored more than one theme. The largest proportion of these examined chemical and nutritional factors (heavy metal exposures and mineral deficiencies). Figure 3 shows the frequency of articles published, by research area and publication period. Most articles were published between 2009 and 2013, with the exception of articles on vaccines, most of which were published between 2003 and 2008.

Chemical dimension

The chemical factors we investigated in association with ASD included environmental chemicals, vaccines, medication and substance abuse. Articles on exposure to environmental chemicals and vaccines (both primarily concerning postnatal exposure) each accounted for approximately 40% of the chemical dimension (Figure 2).

Environmental chemicals

The environmental chemicals we examined in association with ASD were predominantly heavy metals, found in biological samples from children, followed by air pollutants; both mainly investigated in case-control studies (Table 2). A small number of the studies and/or reviews explored associations with prenatal or perinatal exposure to occupational chemicals[18,19] and pesticides.[20,21]

Heavy metals

Many studies examined biomarkers of postnatal exposure to heavy metals, particularly mercury, in children with ASD or autism compared to children without ASD. Assessing baby teeth, particularly tooth enamel, which begins to form in utero and continues up to one year after birth,[22] can also help determine prenatal exposure. The five most commonly studied heavy metals were mercury, lead, cadmium, aluminum and arsenic.

Mercury: biomarkers and sources of exposure

Mercury has received considerable attention because of the similarities in the symptoms of mercury poisoning and autism.[23] Biomarkers of mercury exposure in children with autism were primarily examined by measuring levels in hair (14 studies), blood (4), urine (4), teeth (2) and nails (1). However, findings were largely inconsistent (Table 3). Urinary porphyrins, intermediates in heme biosynthesis, have also been studied as potential biomarkers for mercury exposure in people with autism, as increased porphyrins have been associated with prolonged mercury exposure.[24] Elevated porphyrins have been found in children with autism compared to children without autism,[25-29] and may increase with severity of autistic symptoms.[30,31] Although nearly all studies attributed these findings to mercury exposure, none actually measured mercury exposure except for one study, which found no association with ASD despite finding a correlation between elevated porphyrins and ASD.[27]

Few of the studies in this review investigated mercury exposure from sources other than thimerosal in vaccines and Rh immune globulins. Ecological studies have demonstrated an association between environmentally released mercury emissions and significant increases in autism rates,[32] which may be related to residential distance from mercury pollution sources such as industrial or power plant facilities.[33] Other studies have examined other prenatal and postnatal mercury exposure sources in relation to ASD, such as maternal dental amalgam fillings[27,34,35] and maternal or child consumption of seafood,[27,36,37] with inconsistent findings.

A 2012 systematic review concluded that, due to methodological issues such as small sample size and inconsistent case ascertainment, the relationship between mercury exposure and ASD remains unclear.[38] Furthermore, according to a meta-analysis, hair mercury analysis may not be reliable.[39] The use of blood or hair mercury levels as accurate measures of

FIGURE 1
Process for searching and screening research on autism spectrum disorders found in three electronic databases, published between 2003 and 2013

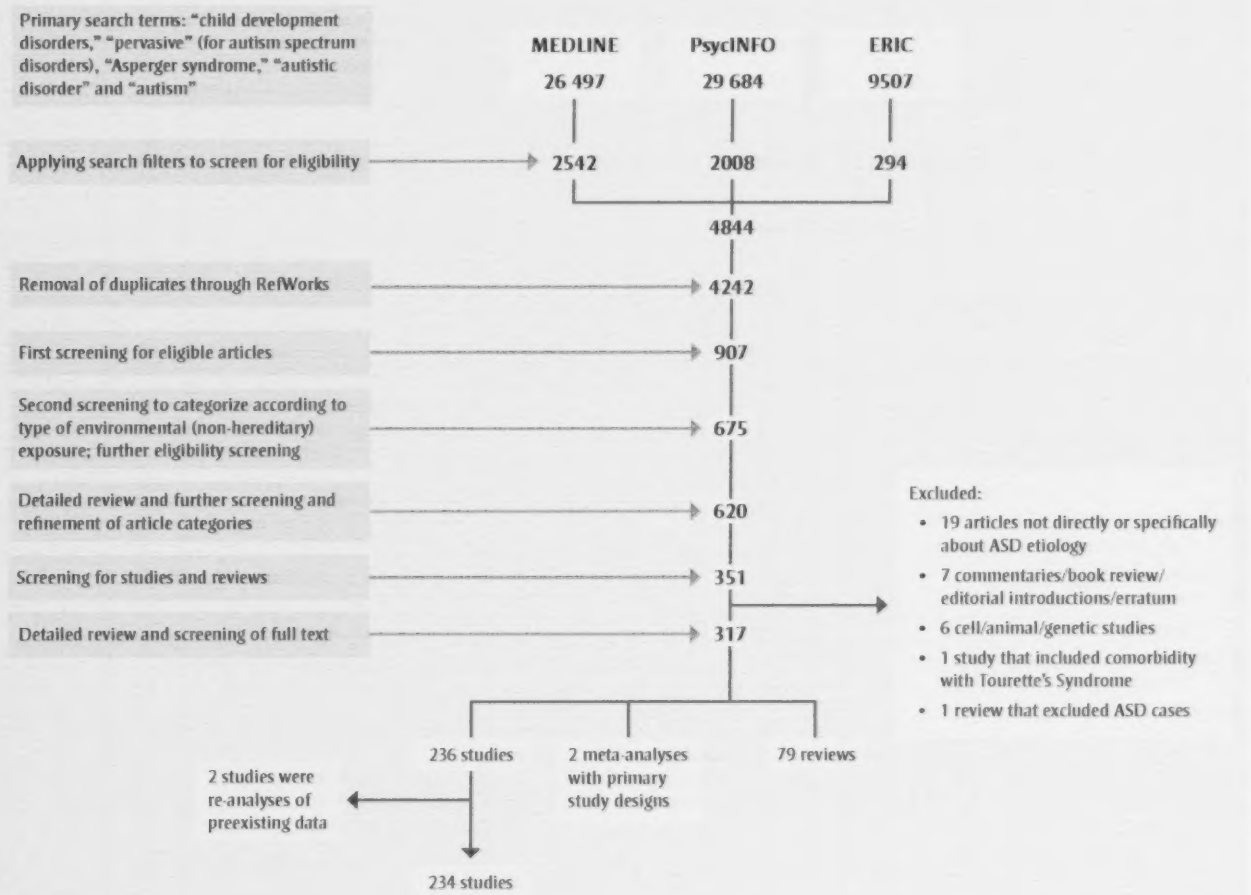

Primary search terms: "child development disorders," "pervasive" (for autism spectrum disorders), "Asperger syndrome," "autistic disorder" and "autism"
MEDLINE
26 497
PsycINFO
29 684
ERIC
9507
Applying search filters to screen for eligibility
2542
2008
294
4844
Removal of duplicates through RefWorks
4242
First screening for eligible articles
907
Second screening to categorize according to type of environmental (non-hereditary) exposure; further eligibility screening
675
Detailed review and further screening and refinement of article categories
620
Screening for studies and reviews
351
Detailed review and screening of full text
317
Excluded:
• 19 articles not directly or specifically about ASD etiology
• 7 commentaries/book review/ editorial introductions/erratum
• 6 cell/animal/genetic studies
• 1 study that included comorbidity with Tourette's Syndrome
• 1 review that excluded ASD cases
236 studies
2 meta-analyses with primary study designs
79 reviews
2 studies were re-analyses of preexisting data
234 studies

TABLE 1
Final selection of 315 research articles on associations between environmental factors and autism spectrum disorder, by dimension and article type

Dimension	# of studies	# of reviews
Chemical	94	44
Physiological	125[a]	36
Nutritional	23	10
Social	25	7
Other	4	2

Note: Some studies/reviews explored more than one theme, and some studies also had a meta-analysis component—totals do not add up to 315.

[a] 124 unique studies. Two studies used the same data.

prenatal and early-life exposure is questionable[38] considering mercury's relatively short half-life.[40,41]

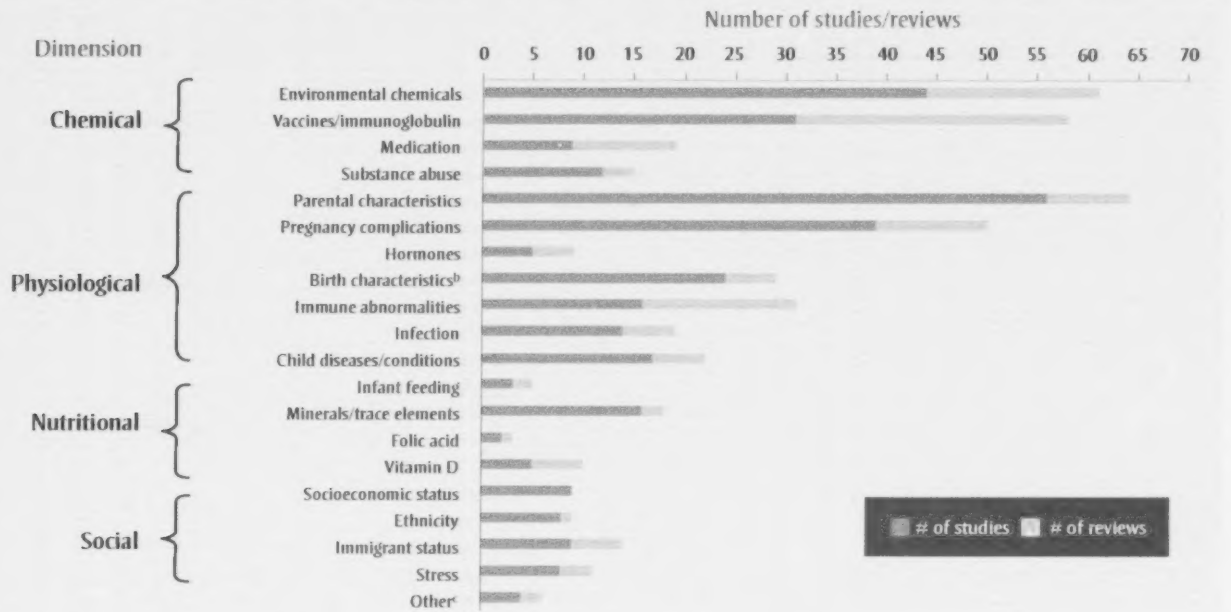
Other heavy metals

Sixteen studies examined the association between exposure to other heavy metals and ASD or autism by measuring levels mainly in hair samples. Lead, cadmium, aluminum and arsenic were the most-studied heavy metals in children with ASD or autism, but there were conflicting findings (Table 3). Most studies found no significant association between aluminum and ASD. None of these studies investigated possible exposure sources.

Pollutants

Only a few studies investigated the relationship between drinking water content and autism.[42,43] However, five population-based case-control studies, mostly in California, investigated air pollutant exposure while controlling for sociodemographic factors. Relatively consistent evidence for an association between prenatal, perinatal and/or early-life traffic-related air pollutant exposures and ASD or autism was found[44-48] (Table 4). Exposure to traffic-related air pollution can result in respiratory and cardiovascular disease and certain neurological outcomes by triggering inflammation and oxidative stress,[49-51] which are common physiological abnormalities observed in children with ASD. Maternal residence in areas with higher levels of exposure to nitrogen dioxide,[44,47] exposure to particulate matter less than 2.5 μm[44,47] and exposure to nitric oxide[44]

FIGURE 2
Final selection of articles[a] on associations between environmental factors and autism spectrum disorder, by subject and article type



[a] Includes an article that was a primary research study and a meta-analysis.

[b] Includes birth order/parity, spacing, seasonality and multiple births.

[c] Includes prenatal ultrasound, electromagnetic radiation and geographical clustering.

during gestation and/or the early life of the child were associated with having a child with autism. Also, residing near a freeway during pregnancy, especially during the third trimester, was associated with having children with autism.[46] Findings for prenatal exposure to other pollutants including ozone and particulate matter less than 10 μm[44,47] or prenatal and/or perinatal exposure to specific chlorinated solvents and metals[45,48] in relation to autism or ASD have been inconsistent so far.

Vaccines and medication

Vaccines

Measles Mumps Rubella (MMR) vaccination

Since the publication of the Wakefield case series study,[52] which found an increased prevalence of a new variant of autism characterized by gastrointestinal disorders and developmental regression, the safety of MMR vaccine has been questioned, although this paper was later retracted due to false data. Nine case-control and two time-series studies[53-63] and two systematic reviews[64,65] found no significant association between MMR vaccine and ASD or autism, although another time-series study did.[66] A systematic review found that studies with the lowest bias based on study quality criteria did not support a causal association.[64] Evidence for an association between the new variant form of ASD[58,59,65] and MMR vaccine, and between measles infection and autism,[64,67] was also lacking.

Thimerosal containing vaccines and immune globulins

Thimerosal, a preservative that contains 50% ethylmercury and is used for multivial vaccines such as the diptheria-tetanus-pertussis vaccine, has been widely researched because of concerns about mercury overexposure stemming from the expansion of childhood vaccination schedules in the past several decades. Thimerosal in Rh immune globulins given to pregnant women with Rh incompatibility issues has also been investigated as a source of prenatal mercury exposure.

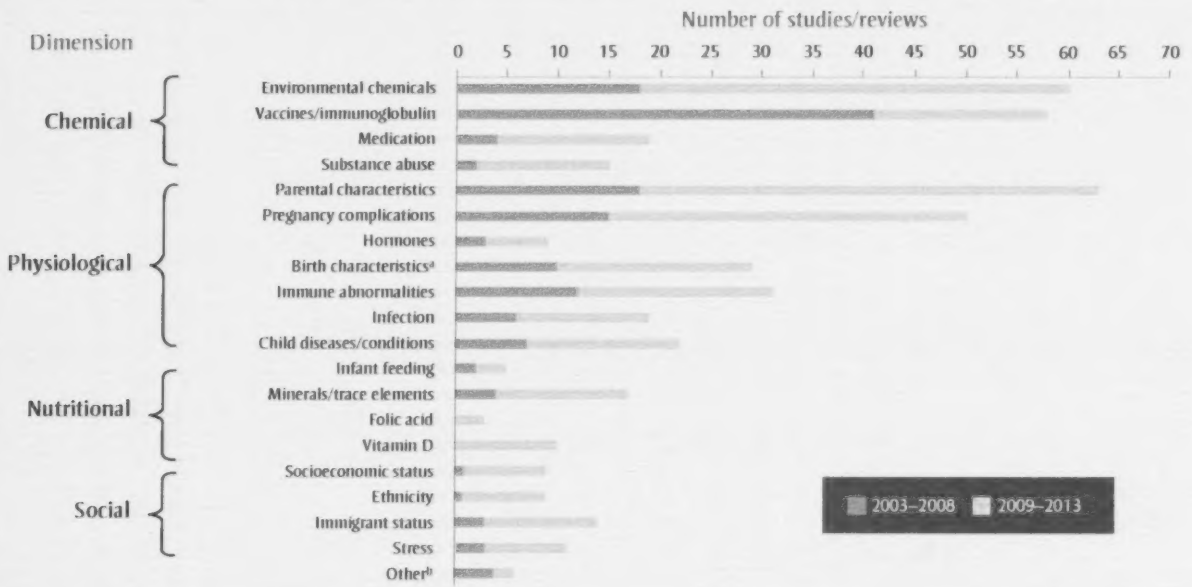
Postnatal thimerosal exposure: early childhood vaccines

Seven studies demonstrated no significant association between thimerosal-containing childhood vaccines and ASD,[68-74] while four studies did.[66,75-77] However, most of the studies that supported an association, which all came from the same authors, did not control for potential confounders such as the child's age and sex, in contrast to most studies that found a null association. Both cohort studies that found significant positive associations used the Vaccine Adverse Events Reporting System database, which has been criticized as potentially biased and unreliable because anyone can report an adverse event after vaccination and diagnoses are not medically validated.[78] Furthermore, no association has been found between autoimmune markers and autism in children given thimerosal-containing vaccines.[79,80]

Prenatal thimerosal exposure: Rh anti-D immune globulin

Some studies, mostly larger case-control studies, refuted the association between maternal prenatal exposure to thimerosal-containing Rh immune globulin and ASD, adjusting for maternal and/or birth characteristics,[37,69,81,82] while others found significant

FIGURE 3
Final selection of articles on associations between environmental factors and autism spectrum disorder, by subject and time period, 2003–2008 and 2009–2013



[a] Includes birth order/parity, spacing, seasonality and multiple births.

[b] Includes prenatal ultrasound, electromagnetic radiation and geographical clustering.

associations without adjusting for potential confounders.[83,84]

Medication

The increasing use of antidepressants, antibiotics[85] and acetaminophen[86] has sparked hypotheses of possible links with the use of these medications and synchronous rising ASD prevalence in the 1980s.

Research on selective serotonin reuptake inhibitors (SSRIs; a class of antidepressants) in relation to ASD has emerged recently, with reviews indicating biologically plausible evidence of an association from animal and preclinical studies.[87,88] Two case-control studies found a moderate association between prenatal use of SSRIs and ASD.[89,90] However, if the relationship was causal, prenatal antidepressant use would account for fewer than 1% of ASD cases.[90]

Three reviews cited several clinical studies that provided evidence for increased ASD prevalence among children exposed to valproic acid (or valproate), a teratogenic broad spectrum antiepileptic drug and mood stabilizer, in early pregnancy compared to unexposed children.[91-93] Additionally, a large prospective cohort study showed that prenatal valproate exposure was associated with an absolute risk of ASD of 4.42% over a 14-year period among those exposed.[94]

Some studies suggested a possible link between prenatal or early-life antibiotic use and autism.[85,95,96] Studies found ecological associations with prenatal use of acetaminophen[97] and circumcision rate (a proxy for acetaminophen, which was widely used following circumcision),[97] and an association with acetaminophen use following MMR vaccination.[98] Biologically plausible mechanisms related to the endocannabinoid system affecting central nervous system (CNS) development[98,99] or impaired detoxification ability upon overdose[86] have been suggested.

Substance use

Tobacco smoke

A meta-analysis has indicated no significant association between smoking during pregnancy and ASD.[100] Likewise, no association was found in later studies.[101-105] However, an association between maternal smoking during pregnancy and subclassifications of ASD, including Asperger syndrome and/or PDD-NOS, has been demonstrated.[106-108] Maternal secondhand tobacco exposure may be associated with ASD or autism in children based on two small case-control studies.[37,109]

Alcohol

Two studies, including a prospective cohort study, found no association between prenatal alcohol consumption and ASD or autism,[106,110] whereas a significant association with heavy prenatal consumption was evident in a small clinic sample.[111]

Physiological dimension

The physiological dimension encompasses many recurring themes related to the physiology of the parents and the child with ASD. Parental characteristics, particularly parental age, and pregnancy complications, especially low birth weight and prematurity, have been the most-studied risk factors for ASD (Table 5).

Parental characteristics

Parental age

Five systematic reviews supported the association between advanced parental

TABLE 2
Chemical factors studied from 2003–2013 in association with autism spectrum disorder, by article type and subtheme

Subtheme	# of studies	# of reviews
Environmental chemicals		1[a]
Heavy metals		
Mercury	31[b]	13[c]
Other heavy metals	15	6
Pollutants		
Air	5	1
Water	2	0
Occupational chemicals	2	0
Pesticides	2	3
Vaccines/medication		
MMR vaccine	13[d]	19
Thimerosal-containing vaccines/Ig	17[e]	16
Other vaccine-related[f]	2	0
Valproate	1	4
Antibiotics	3	1
Acetaminophen	2	4
Terbutaline	1	0
Antidepressants	2	2
Substance abuse		
Alcohol	3	0
Tobacco smoke	10	3

Abbreviations: ASD, autism spectrum disorder; MMR, measles, mumps, rubella; Ig, immune globulin.

Note: Some research articles may have multiple study designs and some studies may have examined multiple exposures; there may be overlap between subthemes.

[a] Review examines environmental chemicals as a whole and does not distinguish between different kinds.

[b] Excludes two studies that re-analyzed data from previously existing published research.

[c] One systematic review examined mercury exposure in general which ultimately included studies on thimerosal exposure.

[d] Two studies assessed association with measles virus infection.

[e] Four studies on prenatal exposure to thimerosal through Rh immunoglobulin, 12 studies on postnatal exposure to thimerosal through child vaccines, and one study on both prenatal and postnatal exposure to thimerosal.

[f] Studies on exposure to aluminum adjuvant, fever following vaccine and mitochondrial disease, and adverse reactions following vaccine.

age and ASD.[13,100,112-114] A 2011 meta-analysis found a pooled odds ratio (OR) for autism of 1.78 (95% confidence interval [CI]: 1.52–2.07) for fathers 40 to 49 years of age compared with fathers aged 29 years or younger.[113] Since the latest systematic review,[13] four studies have found a significant association with ASD or autism,[115-118] whereas one did not.[119] De novo mutations and genomic copy number variations burden have been implicated as possible underlying mechanisms, because they increase with paternal age.[120,121] No association has been found between men with autistic-like traits and delayed parenting.[122,123]

A 2012 meta-analysis found the relative risk (RR) of ASD for mothers aged 35 years or over compared to those aged 25 to 29 years to be 1.31 (95% CI: 1.19–1.45).[114] Since the most recent systematic review,[114] four studies have found significant associations between advanced maternal age and ASD[117,118,124,125] and one did not.[106]

Some studies have found paternal and maternal ages to be independent risk factors for ASD after adjusting for spousal age,[126-128] and no evidence for a synergistic effect.[117] Other studies have accounted for multicollinearity of maternal and paternal ages and found that advanced maternal age was the primary independent contributor of the parental age effect.[118,129,130]

Assisted conception

Assisted conception and ASD share risk factors such as high parental age, high rate of prematurity and low birth weight.[131] A systematic review cited methodological limitations as the source of inconsistent findings for the association between assisted conception and ASD.[132] Since then, two studies have found a positive association between assisted reproductive technology use and ASD,[133,134] whereas five studies have found none.[131,135-138] However, significant positive associations were found among subgroups such as women over age 34,[136] multiple births[137] and those exposed to specific assisted conception methods.[131,135]

Maternal chronic diseases and conditions

Some evidence exists for associations between maternal chronic conditions such as weight gain, obesity and diabetes and ASD. Two[109,139] of four studies found a positive association between maternal chronic conditions (aggregate measure) and ASD or autism.[106,109,139,140] Two[141,142] of three cohort studies[141-143] found a significant association between either prepregnancy weight, pregnancy weight gain or early-life obesity and ASD. A 2009 meta-analysis found a positive association between maternal gestational diabetes and ASD.[100] Since then, there have been conflicting findings,[102,124,139,141,144,145] although some of these studies did not differentiate between prepregnancy and gestational diabetes.

Hormones

Prenatal testosterone

An association between elevated prenatal testosterone levels and ASD or autism has been implicated in a review of three meta-analyses[146] and a case-control study.[147] However, no significant correlation was found with neonatal testosterone levels in a cohort study.[148]

Thyroid hormone

Thyroid dysfunction, whether due to prenatal or early-life exposure to the anti-thyroid effects of heavy metals, to endocrine-disrupting chemicals or to dietary deficiencies, may affect neurodevelopment.[149-151] However, evidence for the association between neonatal or maternal levels of thyroid hormone and ASD is limited and inconsistent.[152-154]

Pregnancy complications

A 2012 systematic review found perinatal and neonatal pregnancy complications to be significantly associated with ASD.[13] However, findings were inconclusive for eclampsia and/or pregnancy-induced hypertension. Findings were also inconsistent among several other studies.[102,103,124,125,145,155,156]

Birth weight and gestational age

Two systematic reviews[112,157] found low birth weight to be a significant risk factor for ASD in children; one of them, a meta-analysis, found a risk ratio (RR) of 1.63 (95% CI: 1.19–2.33).[157] However, a more recent systematic review[13] indicated mixed findings. Since then, three[158-160] of five studies[106,109,158-160] have found a significant association between low birth weight and ASD. In most studies, the low birth weight threshold was 2500 g.

Two[13,112] of three systematic reviews[13,112,157] supported the association between low gestational age and ASD. Since the 2012 systematic review,[13] most studies have provided more evidence for this

TABLE 3
Associations of heavy metals in children with autism spectrum disorder or autism, found in studies and/or reviews published 2003–2013

Metals	Number of associations			Comments
	Positive	Negative	NS	
Mercury	11	4	11	**Findings:** Trending toward positive or null findings.
	Ref.:	Ref.:	Ref.:	**General information on mercury**
	1. Majewska et al. (2010)[260]	1. Majewska et al. (2010)[260]	1. Rahbar et al. (2012)[118]	**Sources of exposure[a]:**
	2. Geier et al. (2010)[261]	2. Holmes et al. (2003)[34]	2. Wright et al. (2012)[226]	• Mainly methylmercury (organic mercury) from contaminated fish/seafood.
	3. DeSoto and Hitlan (2007)[262]	3. Obrenovich et al. (2011)[216]	3. Williams et al. (2008)[265]	• Inorganic mercury from sources such as dental amalgam much lower. Inhalation of mercury vapours in air from industries that burn mercury-containing fuels and from occupational exposures.
	4. Adams et al. (2007)[95]	4. DeSoto and Hitlan et al. (2007)[262]	4. De Palma et al. (2012)[225]	
	5. Fido and Al-Saad (2005)[263]		5. Albizzati et al. (2012)[266,b]	
	6. Blaurock-Busch (2012)[219]		6. Kern et al. (2007)[267]	
	7. Blaurock-Busch et al. (2011)[37]		7. Abdullah et al. (2012)[229]	**Trends[a]:**
	8. Al-Ayadhi (2005)[223]		8. Blaurock-Busch et al. (2011)[37]	• Use of mercury in consumer products decreased due to phasing out of most products (e.g. thermometers).
	9. Priya and Geetha (2011)[220,c,d]		9. Woods et al. (2010)[27]	• Use in light bulbs increased due to widespread use of compact fluorescent bulbs.
	10. Geier et al. (2012)[264,d]			**Overall assessment:**
				• Inconclusive findings.
				• Studies do not identify exposure sources nor form of mercury (organic or inorganic).
Lead	9	2	8	**Findings:** Trending toward either positive or null findings.
	Ref.:	Ref.:	Ref.:	**General information on lead**
	1. Fido and Al-Saad (2005)[263]	1. Kern et al. (2007)[267]	1. Vergani et al. (2011)[215]	**Sources of exposure[a]:**
	2. El-Ansary et al. (2011)[268]	2. Yorbik et al. (2010)[228]	2. De Palma et al. (2012)[225]	• Food, drinking water, soil and household dust due to natural abundance in environment.
	3. Al-Farsi et al. (2013)[222]		3. Adams et al. (2007)[95]	• Water pipes in older homes may contain lead solder.
	4. Blaurock-Busch et al. (2012)[219]		4. Albizzati et al. (2012)[266,b]	• Children may be exposed by eating lead-based paint chips or playing in lead-contaminated soil.
	5. Priya and Geetha (2011)[220,c]		5. Abdullah et al. (2012)[229]	• Inhalation of contaminated dust likely from occupational environments.
	6. Blaurock-Busch et al. (2011)[37,c]		6. Wright et al. (2012)[226]	**Trends[a]:** Since the early 1970s, lead exposure in Canada has decreased dramatically, primarily because of phasing out leaded gasoline and lead-based paints, and elimination of lead solder in food cans.
	7. Al-Ayadhi (2005)[223]			**Overall assessment:**
				• Inconclusive findings.
				• Due to decreasing lead exposures, the risk is low in Canada.

Continued on the following page

TABLE 3 (continued)
Associations of heavy metals in children with autism spectrum disorder or autism, found in studies and/or reviews published 2003–2013

Metals	Number of associations			Comments
	Positive	Negative	NS	
Cadmium	5	2	7	**Findings:** Trending toward either positive or null findings.
	Ref.:	Ref.:	Ref.:	**General information on cadmium**
	1. Vergani et al. (2011)[215]	1. Kern et al. (2007)[267]	1. Albizzati et al. (2012)[266,b]	**Sources of exposure[a]:**
	2. Al-Farsi et al. (2013)[222]	2. Yorbik et al. (2010)[228]	2. Fido and Al-Saad (2005)[263]	• Mainly food (e.g. leafy vegetables, grains) and occupational sources. Exposure to cadmium is low in all foods.
	3. Blaurock-Busch et al. (2012)[219]		3. De Palma et al. (2012)[225]	• Drinking water and consumer products (e.g. batteries, plastics) in minor amounts.
	4. Blaurock-Busch et al. (2011)[37]		4. Blaurock-Busch et al. (2011)[37]	• Cigarette smoke is a major source for smokers.
	5. Al-Ayadhi (2005)[223]		5. Wright et al. (2012)[226]	**Overall assessment:**
				• Inconclusive findings.
				• Smokers at higher risk of exposure.
				• Inorganic cadmium is associated with lung cancer, severe gastrointestinal irritation and kidney problems at high levels.
				• Studies do not identify exposure sources or form of cadmium.
Aluminum	3	0	8	**Findings:** No significant association with aluminum in most studies.
	Ref.:		Ref.:	**General information on aluminum**
	1. Blaurock-Busch et al. (2011)[37]		1. Blaurock-Busch et al. (2011)[37]	**Sources of exposure[a]:**
	2. Blaurock-Busch et al. (2012)[219]		2. Fido et al. (2005)[263]	• Mainly from food and oral intake of medication containing aluminum (e.g. antacids). Average adult consumes 7–9 mg aluminum per day in food.
	3. Al-Farsi et al. (2013)[222]		3. Albizzati et al. (2012)[266,b]	• Inhalation and dermal contact contribute small amount of daily exposure.
			4. Al-Ayadhi et al. (2005)[223]	• Exposure to small amounts of aluminum from vaccinations.
			5. Vergani et al. (2011)[215]	• High level of exposure to aluminum (likely occupational source) may result in respiratory and neurological problems.
			6. De Palma et al. (2012)[225]	**Overall assessment:** Likely no association between aluminum and ASD.

Continued on the following page

association[145,159,161-163] although two studies did not.[106,125] Based on the positive studies and the systematic review,[13] the effect estimates for ASD or autism ranged from 1.4 to 4.7. The 37-week cut-off to define "preterm" births and the 32-week cut-off to define "extremely preterm" births were used in many studies.

Systematic reviews[13,157] along with subsequent studies[159,161] have also found a significant association between small for gestational age and ASD. Other studies have suggested that a deviance in fetal growth[165] and physical development[140] may be associated with ASD onset.

Clustering of pregnancy complications

Eleven studies, including four cohort studies, found clustering of pregnancy complications to be significantly associated with ASD,[102,104,106,109,124,141,143,166-169] and only one case-control study did not.[140] Four systematic reviews also supported this association,[13,100,112,157] with a general consensus that the presence of multiple factors is associated with ASD. However, the types of pregnancy complications examined vary by study. Many studies have explored the association between optimality scores (composite measures of compromised prenatal, perinatal and neonatal health overall) and ASD. Systematic reviews[100,157]

TABLE 3 (continued)
Associations of heavy metals in children with autism spectrum disorder or autism, found in studies and/or reviews published 2003–2013

Metals	Number of associations			Comments
	Positive	Negative	NS	
Arsenic	5	1	3	**Findings:** Most study samples found positive association although inconsistencies exist.
	Ref.:	Ref.:	Ref.:	**General information on arsenic**
	1. Al-Ayadhi (2005)[223]	1. Kern et al. (2007)[167]	1. Blaurock-Busch et al. (2011)[17]	**Sources of exposure[a]:**
	2. Blaurock-Busch et al. (2011)[17]		2. Fido and Al-Saad (2005)[163]	• Mainly from food (e.g. meat and fish), but also from drinking water, soil, air, and household dust, although exposure usually low.
	3. Blaurock-Busch et al. (2012)[219]		3. De Palma et al. (2012)[225]	• Drinking water may be a major source for populations living near arsenic source.
	4. Obrenovich et al. (2011)[216]			• Arsenic present in cigarettes, although exposure minor.
	5. Vergani et al. (2011)[215]			• High-level exposures usually occupational, near hazardous waste sites, or areas with high natural levels.
				Overall assessment:
				• Inconclusive findings.
				• High-level inorganic arsenic exposure is a health concern. Long-term exposure is of carcinogenic potential.
				• Form of arsenic detected in these studies unknown.

Abbreviations: NS, not significant; Ref., references.

Note: Studies may examine associations with different heavy metals and/or specimens.

[a] Ref.: Health Canada[20,170] and Agency for Toxic Substances and Disease Registry.[10,171,173]

[b] Blood, urine and hair tested with same results.

[c] Hair and nails tested with same results.

[d] Indicates an association with ASD severity.

[e] Urine and hair tested with same results.

have found that reduced prenatal and neonatal optimality is more evident than perinatal suboptimality in ASD cases. However, since those reviews, a prospective cohort study has found that having at least four obstetric suboptimality factors (mainly prenatal and perinatal) in the first birth were significantly correlated with ASD.[124] Three other studies have found that suboptimal birth conditions[101,105,141] and/or prenatal pregnancy complications[102,106,141] were more common in children with ASD than in children without ASD.

Systematic reviews[112,157] have implicated fetal hypoxia (intrauterine deprivation of oxygen) in ASD etiology, based on several perinatal factors that may serve as markers of hypoxia, including low Apgar score, caesarean section and growth retardation. However, fetal hypoxia has been weakly associated with ASD according to a population-based cohort study.[170]

Birth characteristics

Birth order and spacing

Systematic reviews agree that first-born children are more likely to be diagnosed with ASD than children born third or later;[13,100] the meta-analysis found a 61% increased risk of autism for first-born children compared to children born third or later.[100] This is also consistent with more recent studies,[106,140,171,172] one of which investigated only Asperger patients.[171] Suboptimal parity (giving birth more than two times) has been associated with ASD.[124] Earlier birth order and greater parity appear to be conflicting risk factors, because first-born children in sibship sizes of two, and later-born children in families with larger sibship sizes, are more likely to have ASD.[100] In addition, some studies have indicated that ASD symptom severity may be related to birth order, although these studies did not agree on which place in the birth order was more associated with severe symptoms,[173,174] possibly because interpregnancy intervals may also be a factor.[174] Interpregnancy intervals of less than 18 months[141] or less than a year have also been associated with autism in the second-born child.[175]

Other birth characteristics

Multiple births have been associated with ASD according to a meta-analysis[157] as

TABLE 4
Associations of prenatal, perinatal or postnatal exposure to air pollutants in children with autism spectrum disorder or autism, found in studies published 2003–2013

Author (year)	Sample size Characteristics	Exposure	Outcome	Associations	
				Positive	NS
Becerra et al. (2013)[44]	7603 cases 10 controls/case Age 3–5 years LA, California	Prenatal exposure to traffic pollutants: CO, NO_2, NO, O_3, PM_{10}, $PM_{2.5}$ in mother's residence	Autism	O_3 $PM_{2.5}$ NO NO_2	PM_{10} CO
Kalkbrenner et al. (2010)[45]	383 cases 2829 controls (speech/language impaired) Age 8 years North Carolina West Virginia	Perinatal exposure to ambient metal, particulate and volatile organic air pollutants in census tract of child's birth residence	ASD	Quinolone Styrene	PAH Vinyl chloride Trichloroethylene Methylene chloride Perchloroethylene Mercury Cadmium Nickel Arsenic Lead Toluene Diesel particulate matter
Volk et al. (2011)[46]	304 cases 259 controls (frequency matched by sex, age, geographic area) Age 2–5 years California	Distance to nearest freeway and distance to nearest major road	Autism	Living near freeway (≤ 309 m) during whole pregnancy and third trimester	—
Volk et al. (2013)[47]	279 cases 245 controls (frequency matched by sex, age, geographic area) Age 2–5 years California	Prenatal and 1st year of life exposure to traffic air pollutants: $PM_{2.5}$, PM_{10}, O_3, NO_2	Autism	High quartile exposure to pollutants NO_2, $PM_{2.5}$, PM_{10} during gestation and 1st year	O_3
Windham et al. (2006)[48]	284 cases 657 controls (matched 2:1 by sex and birth month) 1994 birth cohort San Francisco Bay Area	Prenatal and early life exposures to hazardous air pollutants	ASD	**Metals** (highest contribution from mercury, cadmium, nickel) **Chlorinated solvents** (contributed by trichloroethylene, vinyl chloride) **Diesel particulate matter**	Methylene chloride Perchloroethylene Arsenic Lead Manganese Chromium Aromatic solvents

Abbreviations: ASD, autism spectrum disorder; CO, carbon monoxide; NS, not significant; O_3, ozone; NO, nitric oxide; NO_2, nitrogen dioxide; PAH, polycyclic aromatic hydrocarbon; $PM_{2.5}$, particulate matter < 2.5μm; PM_{10}, particulate matter <10 μm.

well as a cohort study,[176] whereas an ecological study did not find an association.[177] A meta-analysis also found a significant association between summer births and ASD.[157] However, conflicting findings are evident in several studies.[144,178-181]

Immune abnormalities

According to a review of research trends, immune dysregulation has been widely studied and possesses the strongest evidence base of the physiological abnormalities in ASD.[12] Early evidence found a potential link between ASD and two main types of immune dysfunction: autoimmunity and brain inflammation.[182] In addition, significantly reduced neonatal blood immunoglobulin G has been observed in archived specimens from newborns subsequently diagnosed with ASD relative to

TABLE 5
Physiological factors studied from 2003–2013 in association with autism spectrum disorder, by article type and subtheme

Subtheme	# of studies	# of reviews
Parental characteristics		
Parental age	39	7
Assisted conception	8	1
Maternal chronic conditions:	16	2
Aggregate	3	0
Diabetes[a]	10	2
Weight/pregnancy weight gain	4	0
Pregnancy complications		
Low birth weight	16	6
Low gestational age	19	6
Post-term birth	2	1
SGA or LGA	6	2
Fetal growth[b]	2	0
Clustering of complications	12	6
All complications	39	11
Hormones		
Testosterone	2	1
Thyroid	3	3
Birth characteristics		
Birth order/spacing	15	4
Multiple births	3	1
Birth seasonality	7	2
Immune abnormalities		1[c]
Autoimmune disease	10	8
Brain inflammation	5	10
Other	1	0
Infection	14	5
Associated child diseases/conditions		
Neonatal jaundice	6	3
Epileptic disorders	5	2
Oxidative stress	6	2

Abbreviations: GA, gestational age; LGA, large for gestational age; SGA, small for gestational age.

Note: There is some overlap of subthemes across different studies/reviews.

[a] Prepregnancy and/or gestational diabetes.

[b] Composite measure of birth weight and GA; head circumference in low-birth-weight and GA children.

[c] Review does not distinguish between different immune abnormalities.

newborns not subsequently diagnosed with ASD.[183]

Autoimmune diseases

Several studies have examined the role of autoimmunity in ASD. Three case-control studies have consistently demonstrated that antibody reactivity to human fetal brain protein is more prevalent in mothers of children with ASD or specifically autism than in mothers of children who do not have ASD or specifically autism.[184-186] Additionally, there may be increased serum folate receptor autoantibodies in children with low-functioning autism with or without neurological deficits relative to control subjects without autism.[187] This suggests that folate transfer to the fetus during pregnancy may be blocked, which may increase risk of neural tube defects.[188] Because these elevated autoantibodies were also present in at least one parent of children with autism, parental antibodies may contribute to autism etiology.[189]

Two cohort studies and a case-control study found an association between maternal or family history of autoimmune diseases and ASD[124,190] or autistic regression,[191] whereas another case-control study found no association.[192] However, the specific autoimmune diseases associated with ASD varied by study. Reviews have discussed growing evidence for the role of autoimmunity in ASD, stemming mostly from animal models and human clinical studies, but have indicated a need to identify the functions of the autoantibodies that might be affecting neurodevelopment.[193-196]

Brain inflammation

Brain inflammation has also been implicated in the etiology of ASD. According to the reviews based mainly on animal and human clinical studies, early-life immune insults such as toxic substances, food additives or stress may result in a cascade of excitotoxicity in the brain,[197-199] and may be related to dysregulation of glutamate neurotransmission.[199,200] This cascade may trigger production of proinflammatory cytokines, resulting in chronic inflammation affecting neurodevelopment.

Emerging evidence, mostly from case-control studies, has shown that increased proinflammatory cytokine production is found in the serum or cerebrospinal fluid of ASD children or the amniotic fluid of their mothers,[201-203] although a decreased neonatal level of cytokines has also been observed.[204] Significantly altered adaptive cellular immune function in children with ASD may reflect defective immune activation, which may in turn be associated with ASD impairment.[203] Also, no significant differences have been reported for levels of certain chemokines in neonatal blood and amniotic fluid,[201,205] except in a subgroup with an ASD diagnosis based on the most recent diagnostic criteria.[201]

Infection

Infections may trigger the chronic inflammation of the CNS, affecting brain development and maturation, which has been implicated in ASD etiology.[198] However, according to a meta-analysis[189] and 2012 literature review,[206] there was no significant association between maternal infection and ASD. A 2012 systematic review indicated that more research is required to explore this association.[13] Since then, only one case-control study found a significant association,[106] whereas one cohort and three case-control studies did not.[96,125,140,207] The definition of maternal infection varies across studies; it may encompass any infection during pregnancy, or only specific infections such as influenza.[207] Some studies have suggested maternal fever during pregnancy[207] or extended febrile episodes[96] are associated with ASD, although findings are mixed.[145,208]

Associated child diseases

Neonatal jaundice

Neonatal jaundice, a result of elevated serum bilirubin levels (hyperbilirubinemia), has been a concern because unconjugated bilirubin can be toxic to the developing CNS. Five studies[125,144,209-211] and two systematic reviews[13,157] investigated this risk factor. According to the systematic reviews, hyperbilirubinemia was associated with an increased risk of autism[13,157] with a summary effect estimate of 1.87 (95% CI: 1.01–3.47), according to the meta-analysis.[157]

Epileptic disorders

While a meta-analysis indicated no significant relationship between neonatal seizures and ASD,[157] four small studies have provided some evidence for a possible association.[125,212-214]

Oxidative stress

According to a review of research trends, oxidative stress was one of the most-studied physiological abnormalities in ASD, with one of the strongest evidence bases, mainly consisting of clinical and animal studies.[12] Six case-control studies

indicated a role for oxidative stress in ASD patients[29,80,215-218] based on different biomarkers of oxidative stress and impaired antioxidant systems. Biomarkers included altered levels of oxidative stress defence systems, including metallothioneins and antioxidant enzymes.[215] Other markers of oxidative stress, associated heavy metal toxicity and/or low detoxification capacity included abnormal markers of thiol metabolism,[216] transsulfuration abnormalities,[80] urinary organic acids,[29] and increased lead and potassium ions, ATPase activity and lipid peroxidation products.[217]

Nutritional dimension

Deficiencies in minerals and levels of trace elements were the most-studied of the nutritional factors in association with ASD, followed by vitamin D deficiency (Table 6).

Minerals and trace elements

Evidence for mineral deficiencies and levels of trace elements in children with ASD or specifically, autism, comes mainly from case-control studies examining hair samples and remains inconclusive. Studies looking at associations between levels of zinc,[37,95,215,219-223] iron,[37,215,216,219,222-224] magnesium,[37,219,220,222,223] copper,[37,215,216,219,220,222,223,225,226] molybdenum,[37,219,222,223,225] nickel,[215,219,222,223,225] and selenium[37,219,220,223,225] and ASD have had conflicting results. Calcium deficiencies have also been documented in association with ASD or autism in children,[219,222,223,227] with some inconsistencies.[37,215] Despite inconsistencies, differences in the levels of cobalt,[37,215,222,223,225,226] chromium[37,215,222,223,225,228] and manganese[37,215,219,223,225,226,229] in children with and without ASD or autism were mostly nonsignificant.

TABLE 6
Nutritional factors studied from 2003–2013 in association with autism spectrum disorder, by article type and subtheme

Subtheme	# of studies	# of reviews
Minerals/trace elements	16	2
Vitamin D	5	5
Infant feeding	3	2
Folic acid	2	1

Note: There is some overlap of subthemes across different studies/reviews.

Vitamin D

Vitamin D plays a crucial role in various functions, such as neurodevelopment, the anti-inflammatory response and the detoxification pathway.[230,231] However, evidence for an association between vitamin D deficiency and ASD is limited and indirect. Two ecological studies[63,232] and a case-control study[227] have indicated an association between vitamin D deficiency in mothers and/or their children with autism, and the onset of autism. It has been suggested that migration may play a role in the etiology of ASD, because of increased autism prevalence rates among immigrants in northern European countries, and because immigrants with dark skin are more prone to vitamin D deficiency due to their skin pigmentation.[233] However, both a small case-control study[234] and a recent Australian prospective cohort study[235] found no significant association between maternal serum vitamin D levels and ASD or a majority of autistic-like traits in their offspring. Furthermore, a systematic review concluded that there was inadequate support for an association, and that more population-based longitudinal studies are needed, given the plausible biological evidence.[230]

Infant feeding

We found few studies on infant feeding methods in relation to ASD, although two case-control studies found that the absence or late initiation of breastfeeding was significantly associated with ASD or autism,[236,237] in contrast to findings of an ecological study.[63]

Folic acid

Evidence supporting an association between folic acid intake and ASD is very sparse, although a recent prospective cohort study found maternal folic acid intake to be protective against ASD,[238] in contrast to an ecological study that found positive correlations between the percentages of prescription prenatal vitamins and pediatric vitamins containing folic acid and ASD incidence.[239]

Social dimension

Socioeconomic status (SES), ethnicity, immigrant status and stress were recurring social factors examined in association with ASD (Table 7).

Socioeconomic status

The importance of SES emerged as a predictor of ASD risk in nine studies,[102,119,172,240-245] but findings were mixed. Mainly in American studies, a higher SES, using proxies such as maternal income, occupation and education, was associated with ASD.[172,240-242] However, when researchers in one of these studies conducted a subanalysis by case ascertainment, no association with SES was found using case ascertainment only from school sources.[242] In an Australian study,[172] maternal residence in remote areas was negatively correlated with cases of ASD without intellectual disability (ID). However, other studies had different results.[102,119,243,244] In countries with universal health care programs, such as Sweden and Canada, lower family or maternal income was associated with ASD, which suggests that the associations between high SES and ASD found mainly in the US studies may reflect inequalities in access to health care services (e.g. under-diagnosis of ASD in families with lower SES).[102,244] Furthermore, spatial analysis of autism incidence in regions of California indicated a higher incidence that was independently characterized by higher levels of parental education.[245]

Ethnicity

Most studies that examined the relationship between maternal ethnicity and ASD found a significant association,[102,119,172,242,243,246] with the exception of one study in the United Kingdom.[247] In particular, maternal minority ethnic status, such as Aboriginal status, was associated with reduced ASD diagnosis in offspring[102,119,172,243] with an OR ranging from 0.33 to 0.83 for certain non-White ethnic groups compared to White, non-Hispanic people. Furthermore, children who were Black, Hispanic or

TABLE 7
Social factors studied from 2003–2013 in association with autism spectrum disorder, by article type and subtheme

Subtheme	# of studies	# of reviews
Socioeconomic status	9	0
Ethnicity	8	1
Immigrant status	9	5
Stress	8	3

Note: There is some overlap of subthemes across different studies/reviews.

"other" race/ethnicity were less likely than White children to have ASD, which was more pronounced in children with ID for some ethnic groups, according to an American study.[246] The finding that minority groups would be less likely to be diagnosed with ASD may be due to ascertainment bias. Differential assessment of children's intellectual and developmental problems may account for these ethnic disparities. In contrast, another American study found that Black race was associated with increased odds of ASD, particularly with ID, but case ascertainment was more likely from school sources.[242] These studies suggest possible racial or ethnic disparities in ASD diagnosis such that for some groups, comorbid ID may affect its detection.

Immigrant status

Maternal immigrant status is another social factor that emerged in eight studies[104,208,243,247,251] and two systematic reviews[13,100] supporting an association with ASD or ASD subtype. Migrant mothers had a higher prevalence of offspring with ASD in studies from Sweden, the United Kingdom and Australia. The meta-analysis found a marginal association between maternal immigrant status and autism (summary effect estimate = 1.28; $p = .06$).[100] However, among Nordic countries, the association was statistically significant, with a 58% increased risk among children whose mothers were born abroad.[100] According to a Swedish study, migrant parents from countries with a low ranking on a human development index may be at increased risk of having children with ASD and comorbid ID compared with Swedish-born parents, particularly when migration occurred around time of pregnancy, suggesting a possible link with maternal stress.[249] However, migrant parents from developing countries may have a decreased risk of having children with PDD-NOS or Asperger.[250] Sociopolitical context such as changes in immigration policy has also been shown to influence trends in autism diagnosis rates. For example, a decline in autism rates among Hispanic children in the United States was attributed to undocumented immigrant parents' reluctance to seek diagnostic services due to fears of being reported to the authorities and having to face deportation when threatened by anti-immigrant policy enforcement.[251]

Maternal stress

Prenatal exposure to environmental stressors, including stress-related immunological and neuroinflammatory abnormalities and placental dysfunction that can affect fetal neurodevelopment, may play a role in ASD etiology.[252,253] A 2012 systematic review indicated this association requires more study to provide conclusive evidence.[13] Since then, one cohort study and a case-control study have shown that maternal stress during pregnancy is associated with conceiving a child with ASD,[106,254] whereas three other case-control studies did not find an association.[140,145,255] In many of these studies, "stressors" may be defined broadly as any type of stressful event,[106, 140,145,255] or specifically as certain stressful events such as early-life childhood abuse.[254]

Other

In addition to the chemical, physiological, nutritional and social dimensions, several other factors emerged that were investigated for association with ASD. Two studies showed that autism births occur in geographical clusters, which could indicate that local factors are involved in the prevalence.[247,256] Another study found that while electromagnetic radiation has been hypothesized to be a risk factor due to biological plausibility, no epidemiological evidence is yet available.[257] Other studies have found no significant association between prenatal exposure to ultrasound and ASD.[256,258]

Discussion

Most of the research on the environmental contribution to ASD etiology focussed on physiological or chemical risk factors, and less on social and nutritional factors. Within these dimensions, however, the vast literature is riddled with inconsistent findings. Heterogeneity is evident in study populations, exposure and outcome assessment, changing diagnostic criteria and/or ASD phenotypes, all of which vary between studies and may affect the validity of findings.

Biomarkers of heavy metal exposure, particularly mercury, from levels measured in biological specimens such as hair, blood and urine have been studied intensely, but its association with ASD remains uncertain due to conflicting findings. Because most of these studies only measure biomarkers of heavy metal, and do not ascertain actual exposure sources, temporality of association is unknown. Furthermore, many of the biomarker studies had small sample sizes. These findings are consistent with a recent systematic review by Rossignol and colleagues[11] (published in 2014, after the completion of our review), who examined the association between environmental toxicant exposure and ASD.

In contrast, emerging evidence for the association between traffic-related air pollutants and ASD or autism has been relatively consistent, although further research is required to establish specificity of association and improve external validity beyond the American landscape. These findings are also consistent with Rossignol's review, which found that air pollution is the chemical risk factor with the strongest evidence of an association with ASD, although the association with pesticides was also relatively strong.

Despite numerous studies exploring the relationship between MMR or thimerosal-containing vaccines and ASD, there is a lack of convincing support for this association. Additionally, evidence of an association between fetal or childhood exposure to various medications and ASD is limited to a few studies. A lack of association between tobacco smoke exposure and ASD is also apparent, although some studies have indicated a possible link with PDD-NOS, warranting further study on ASD subgroups separately if causal relationships are to be elucidated. Moreover, studies on exposure to occupational chemicals, pesticides and alcohol were limited.

The most widely and consistently implicated physiological factors in ASD onset include advanced parental age, low birth weight, prematurity and clustering of pregnancy complications. A consistent association between hyperbilirubinemia and ASD has been demonstrated as well. More research is warranted on the effects of advanced grandparental age on ASD, based on preliminary findings.[115,259] Furthermore, studies are needed to understand the mechanisms for associations between these physiological factors and ASD. Emerging epidemiological evidence for immune abnormalities related to autoimmunity and brain inflammation have also been reported in children with ASD or their mothers. However, further work is

required to establish temporality of association and to elucidate their possible role in ASD etiology.

More research is also needed to understand other physiological factors such as birth characteristics, maternal chronic conditions, hormones and child conditions in relation to ASD. Studies have indicated a potential relationship between chronic conditions such as pregnancy weight gain or maternal diabetes and ASD. However, due to heterogeneity and lack of specificity of exposures, further research is warranted. Evidence for a link between earlier birth order, greater parity and short interpregnancy intervals and ASD exists, although the etiological contribution is not clear. The association between oxidative stress and ASD has been demonstrated by a limited number of small epidemiological studies.

The relationship between nutritional factors and ASD has not been well studied compared to that with chemical and physiological factors. Although several studies investigated associations with mineral and/or trace element deficiencies and vitamin D deficiency, evidence is inconsistent and indirect. For example, maternal foreign birthplace and/or ethnicity were used as proxies for vitamin D concentration, based on the possibly inaccurate assumption that women in these categories would have darker skin pigmentation, affecting their vitamin D concentrations.[233] More direct evidence for an association between vitamin D and ASD by direct exposure measurements is required.

The current literature suggests that associations between social factors such as SES and ethnicity and ASD may vary across countries, depending on possible case ascertainment biases. However, maternal immigrant status has been consistently correlated with ASD. Whether this may relate to SES, adaptation to a new environment, stress or changes in vitamin D exposure as suggested by some studies requires further investigation.

Overall, the lack of consistency, temporality and specificity of the associations observed in many studies precludes the establishment of causality. Longitudinal studies may be helpful in establishing temporality to identify possible causal relationships. Consistent methods of measuring exposure and case ascertainment and consideration for potential confounders could reduce heterogeneity. Underlying mechanisms of some of these associations need to be investigated through further biological research.

Strengths and limitations

Of the reviews that have explored possible risk factors of ASD to date, none have examined the entire scope of the environmental contribution to ASD. We conducted a comprehensive, systematic search of the literature. Although all relevant articles may not have been retrieved in this review, a large number of potentially contributing factors were identified that can provide an adequate picture of the breadth of environmental contribution to ASD etiology.

Although the search strategy to retrieve relevant ASD articles aimed for comprehensiveness, key scientific journals were not hand-searched and no searches were performed on citations referenced in included studies and grey literature. Furthermore, more information on environmental factors may have been missed if articles covering them also dealt with animal models or genetic studies, which were excluded. This is evident for research in immune abnormalities and oxidative stress, because articles retrieved were fewer in number although reviews have indicated a vast amount of research, likely from clinical and animal studies. Because the aim of this scoping review was to assess the current state of knowledge of environmental risk factors of ASD, quality assessment of these studies was not performed to assess the strength of evidence.

Conclusion

Our scoping review examined research conducted between 2003 and 2013 on environmental factors potentially associated with ASD, grouped into four categories: chemical, physiological, nutritional and social. We found that physiological factors including advanced parental age, low birth weight, prematurity, hyperbilirubinemia and clustering of pregnancy complications have been consistently reported as risk factors for ASD. While evidence for an association with traffic-related air pollutants is emerging, research on nutritional factors associated with ASD is limited. Of the factors in the social dimension, immigrant status has been consistently associated with ASD, which warrants further research. Other associations with social factors such as SES and ethnicity may reflect disparities in ASD diagnosis. Large prospective studies, adjusting for sociodemographic confounders, are needed to resolve inconsistencies, especially in the area of heavy metal exposure, where evidence for an association with ASD is still inconclusive.

Because there are a variety of associations with ASD, the etiology is likely multifactorial. Future studies should continue exploring how these different factors may be interrelated. Overall, the lack of consistency, temporality and specificity of associations between environmental factors and ASD remains the largest barrier to establishing causal relationships.

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Status report

The Public Health and Planning 101 project: strengthening collaborations between the public health and planning professions

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Tweet this article

Abstract

The Public Health and Planning 101 project aimed to increase cross-disciplinary knowledge among public health and planning professionals involved in the land use planning process. The multi-disciplinary project team administered an online survey in 2012 to Ontario public health and planning professionals in order to identify learning needs related to the built environment that would inform the development of the education module. The survey asked about built environment work, experience with collaborations, barriers faced working with the other profession, and learning needs. Most survey respondents agreed that both professions *should* be working together on the built environment, although only half indicated they actually were. The survey findings revealed the need for an education module to help public health and planning professionals collaborate in the land use planning process in Ontario, and to help inform policy related to healthy built environments.

Keywords: *knowledge translation, intersectoral collaborations, built environment, education module, public health, planning*

Highlights

- This study was undertaken to increase knowledge about barriers to collaboration and learning needs among public health unit staff and planners to help each profession better contribute to healthy built environment policies.
- In 2012, an online survey was developed and administered to public health professionals and professional planners.
- Respondents from both professions indicated limited human resources and limited understanding of each other's mandates as barriers to collaboration. Training will help build capacity among both professional groups on how best to work together.
- As a result of this needs assessment, a free online training program entitled "Public Health and Planning 101: An Online Course for Public Health and Planning Professionals to Create Healthier Built Environments" was launched in 2016 by the Ontario Public Health Association as a collaborative project with the Ontario Professional Planners Institute and the Public Health Agency of Canada.

Introduction

Land use planning is a complex field comprised of legislation, policies, processes and tools. A growing body of evidence supports the relationship between land use planning decisions, community design and health.[1-3] The built environment has been shown to be associated with physical inactivity, obesity, cardiovascular disease, respiratory disease and mental illness.[1-3] Consequently, there is a growing interest within public health to work with planners on land use planning initiatives such as official plans and transportation master plans.[4-8]

As this is an emerging area of collaboration, more education is needed for public health and planning professionals to more effectively work together.[9-11] To meet this need, a volunteer-led collaborative project entitled "Public Health and Planning 101" (the Project) was initiated by the Ontario Public Health Association (OPHA), the Ontario Professional Planners Institute (OPPI) and the Public Health Agency of Canada (PHAC). The purpose of the Project was to increase knowledge about barriers to collaboration and learning needs among public health unit staff and OPPI planners to help each profession better contribute to healthy built environment policies.

The Project included a needs assessment, comprised of a survey, an environmental scan/critical appraisal and an external stakeholder consultation, which in turn informed the development of a Public Health and Planning 101 education module. The module will help planners and public health professionals learn about each other's mandates, roles and responsibilities, and will help identify opportunities for cross-disciplinary collaboration in land use planning. This Project builds on innovative work done by the Public

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Health Services Authority in British Columbia[12] and represents the first needs assessment about barriers to collaboration and learning needs of public health unit staff and registered Ontario planners.

Methods

Two surveys were developed: one for public health professionals and the other for planning professionals (survey questions available upon request to the corresponding author). The surveys were pilot tested in two separate focus group sessions with public health and planning professionals. Focus group volunteers helped to validate the surveys by verifying survey questions, design and overall flow. Feedback was then incorporated into each survey. The final surveys were disseminated in January and February 2012 to Full (Registered Professional Planners) and Provisional OPPI members via email by the OPPI and to public health professionals via public health Listserv email lists.* The two surveys had similar questions that asked about the respondent's knowledge, attitudes and beliefs about the built environment or health, the legislation and mandate of the other profession and the type of resources required for both professions to better collaborate on built-environment and health projects.[1]

Informed consent was obtained from participants through an introduction at the beginning of the survey, which included a description of the Project, an explanation about how information collected would be used and how personal and organizational identifiers would be removed, and a note that participation was voluntary. Confidentiality was maintained for all participants by removing any individual or organization identifiers, and survey results were analyzed and reported as aggregated data and described as a summary of themes. Each survey had an open-ended comments section, and the authors reviewed and organized these qualitative data by category using NVivo version 10 (QSR International Pty Ltd. 2012) or manually. Survey data were saved on a password protected computer at the OPHA office. Since this was a needs assessment, Research Ethics Board approval was not required to conduct this study.

Results

Demographics

In early 2012, 304 public health professionals and 301 planning professionals completed the two separate surveys, comprising the total survey respondents for each respective profession used to calculate proportions. The survey results represent a convenience sample and are not generalizable to the entire population of public health and planning professionals in Ontario.[‡] Results compare survey responses from both groups where appropriate.

Most respondents worked either as public health staff (78%) or planners/senior planners (58%). A smaller percentage of public health and planning professionals worked either as managers (15% and 11%, respectively) or directors (5% and 9%, respectively).

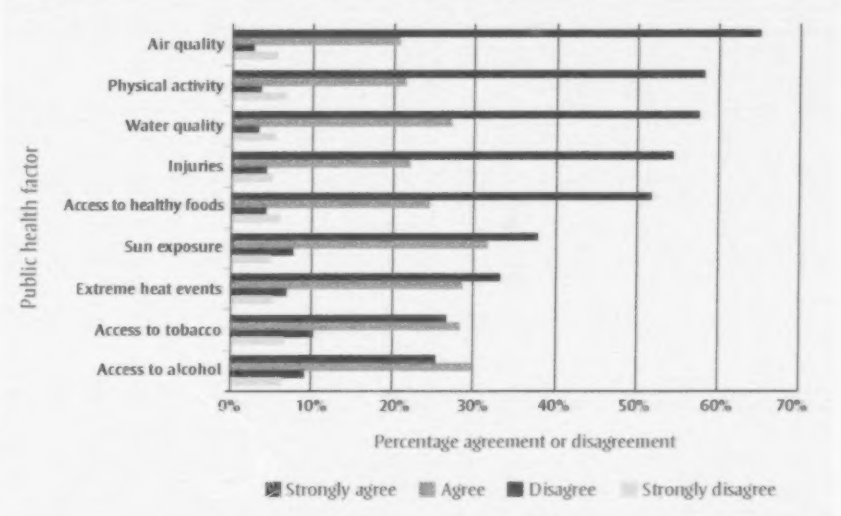
Areas of work impacted by the built environment

Public health and planning professionals both agreed (agree and strongly agree) that air quality, water quality and physical activity were the top three areas of work to be impacted by the built environment (Figures 1a, 1b). Public health professionals agreed that access to tobacco and access to alcohol were impacted by the built environment, but ranked them last, while planning professionals did not agree and ranked them last.

Working together

Approximately half of the public health professionals (52%) and planners (45%)

FIGURE 1A
Extent that areas of work are impacted by the built environment in Ontario, according to public health staff (n = 304)

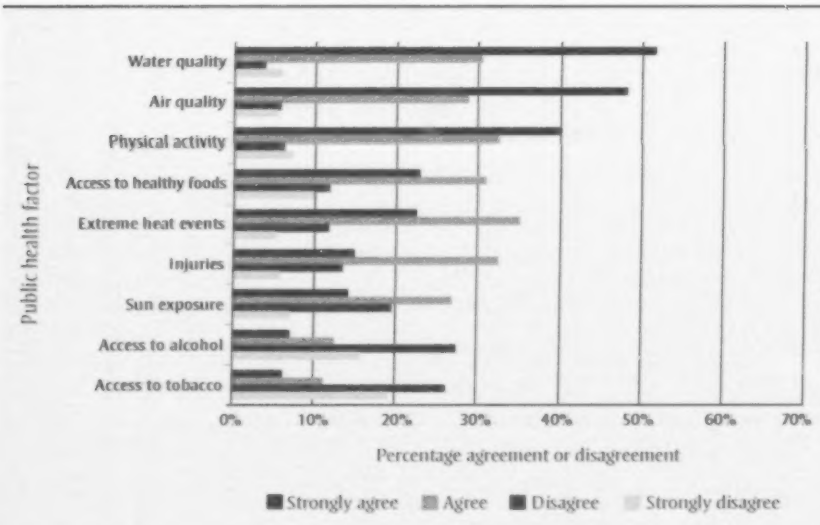


* The public health Listserv email lists included those from the following organizations: OPHA, Association of Public Health Epidemiologists in Ontario, Association of Local Public Health Agencies, Canadian Institute of Public Health Inspectors, Association of Supervisors of Public Health Inspectors of Ontario, Registered Nurses' Association of Ontario, Ontario Society of Nutrition Professionals in Public Health, Health Promotion Ontario, Ontario Nursing Association, and the Council of Ontario Medical Officers of Health.

† The public health survey was only open to public health professionals currently working (in 2012) (or who had worked in 2011) in an Ontario public health unit. Respondents also met one of the following criteria: (i) their work was mandated to address the built environment (as per the Ontario Public Health Standards); (ii) they worked on the built environment; or (iii) they worked as a Director, Medical Officer of Health or Associate Medical Officer of Health. The planner survey was only open to Full and Provisional OPPI members who also met one of the following eligibility criteria: (i) they were working as an employee of a local government in Ontario (or had in the past year); or (ii) they were (or had been in the past year) under a term or project-specific contract with a client that is a local government in Ontario.

‡ The authors attempted to reach all persons eligible to complete the surveys including public health professionals through several Listserv emails and Full and Provisional OPPI members (see Methods section). Respondents had to meet the eligibility criteria before they were able to respond to the survey (see Methods section).

FIGURE 1B
Extent that areas of work are impacted by the built environment in Ontario, according to planners (n = 301)



indicated that they actually worked together on the built environment. However, most public health professionals (95%) and planners (86%) agreed that both professions *should* be working together on the built environment (data not shown). One public health professional commented on the implications of planners and public health professionals working together: "I feel advocating for this concept can have dramatic impact on many aspects of community resident's [*sic*] health — from becoming more active, being more food secure, having cleaner air, and overall a healthier lifestyle in a healthier community."

Ideal roles

Both public health and planning professionals were asked to identify each other's roles on built environment initiatives. Although the proportions were lower for planners compared to public health professionals, both public health professionals and planners identified the following as the two most common roles: "reviews/comments on planning initiatives" (81% and 67%, respectively) and "provides consultation to planning" (74% and 55%, respectively) (data not shown). Fewer planners compared to public health professionals saw these two roles as their own.

Both professions were asked to identify ideal public health staff role(s) when working with planners on the built environment (Figures 2a, 2b). Proportionally, public health professionals and planners recommended most highly the following roles: "provides consultation to planning" (88% and 81%, respectively) and "partners on specific projects" (78% and 66%, respectively). One planning professional commented that it is important to consider how and where to include public health professionals in the planning process.

Barriers to collaboration

Public health and planning professionals were asked to identify barriers that their public health unit or local governments face in working with the other profession on the built environment (Figures 3a, 3b). Barriers included "limited human resources" (63% for public health professionals and 52% for planners), a "lack of understanding regarding application of public health mandate in planning practice" (54% for public health professionals and 59% for planners), and "organizational structures hinder collaboration" (43% for public health professionals and 47% for planners). Half of planners (53%) stated that collaboration with the other profession is "not a priority/requirement," compared to 37% of public health professionals. One public health professional commented on the lack of understanding of each profession's mandate: "We need to learn about what each other does ... [This] may assist in the natural formation of a common ground."

Resource development

Public health and planning professionals were asked about their knowledge of the other profession and the type of learning resource they would find most useful. In relation to land use planning, public health staff indicated that they had the least amount of knowledge about processes, legislation and policy, while planners indicated that they had the least amount of knowledge about legislation, standards and organizational structure. Both public health staff and planners indicated that they had the most extensive knowledge about terminology, roles and responsibilities (Figures 4a, 4b). When public health professionals and planners were asked to specify topics or provide suggestions as to what a resource should

FIGURE 2A
Ideal roles for public health staff working with planners on the built environment, according to public health staff (n = 304)

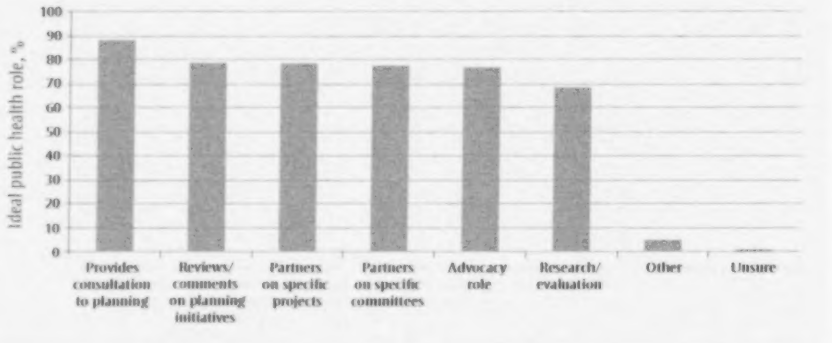


FIGURE 2B
Ideal roles for public health staff working with planners on the built environment, according to planners (n = 301)

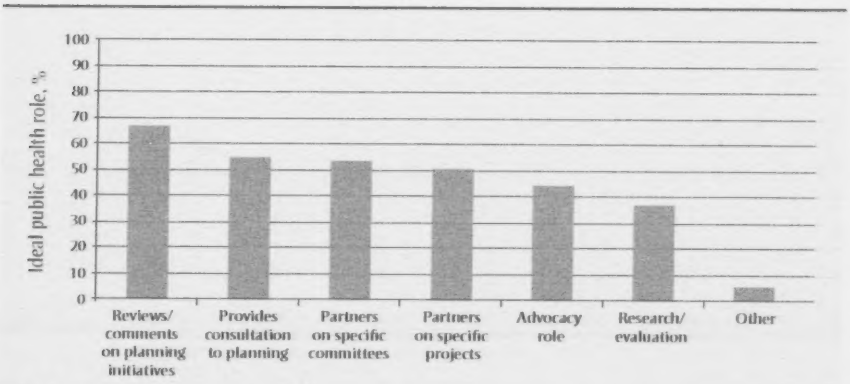


FIGURE 3A
Barriers to working with planners on the built environment, according to public health staff (n = 304)

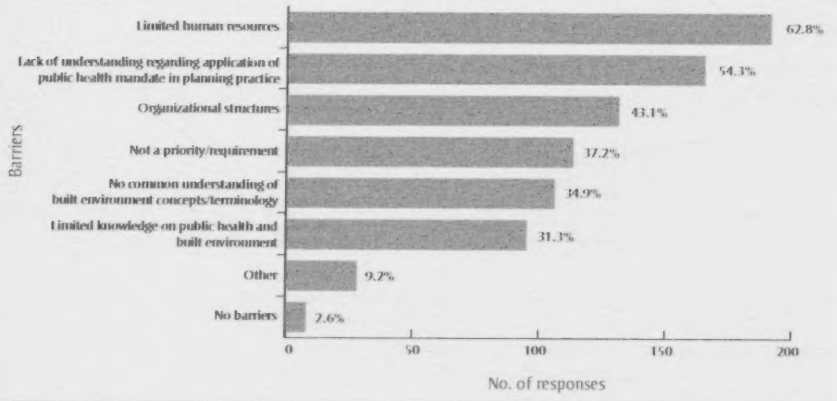
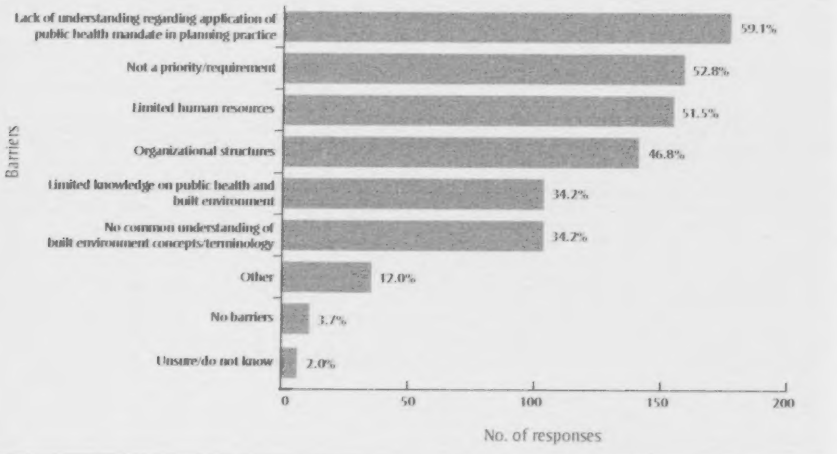


FIGURE 3B
Barriers to working with public health staff on the built environment, according to planners (n = 301)



address, both professions expressed the need for an online learning module that would describe their respective roles, mandates and processes. One planning professional commented that a public health and planning 101 resource would help to "[b]etter understand each discipline's process for making decisions and implementing projects. Glad to see more efforts in combining public health and planning."

Discussion

The survey findings supported the development of a Public Health and Planning 101 online educational module. Despite being in agreement that public health and planning professionals should be working together on the built environment, both professions identified limited human resources and limited understanding of each other's mandates as barriers to collaboration. Survey results suggest that future resources should address barriers that hinder the understanding of each profession's mandates, roles and responsibilities, processes, legislation and policy (or standards), and terminology/concepts related to public health and the built environment.

Given the increased interest and shift towards considering health in land use planning, there is a need to ensure that planners and public health professionals can effectively work together to enhance land use planning in Ontario. The survey findings demonstrate that training is required to build capacity among both professional groups on how to best collaborate.

Conclusion

Health is associated with how communities are planned and built, and the services and resources provided within them. Inspired by the results of our survey and based on user feedback from the pilot tests, a free online training program entitled "Public Health and Planning 101: An Online Course for Public Health and Planning Professionals to Create Healthier Built Environments" was launched in 2016 by OPHA as a collaborative project with OPPI and PHAC. This course is designed to bridge the gaps between the two professions, as well as provide greater opportunities for developing collaborative partnerships to help create and foster healthy built environments. The course is

FIGURE 4A
Extent of their knowledge on land use planning, according to public health staff (n = 304)

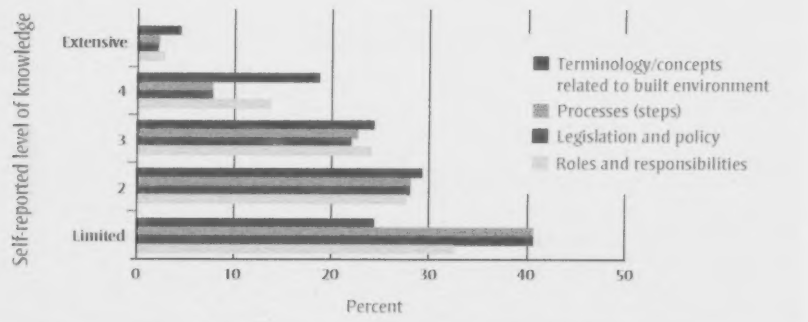
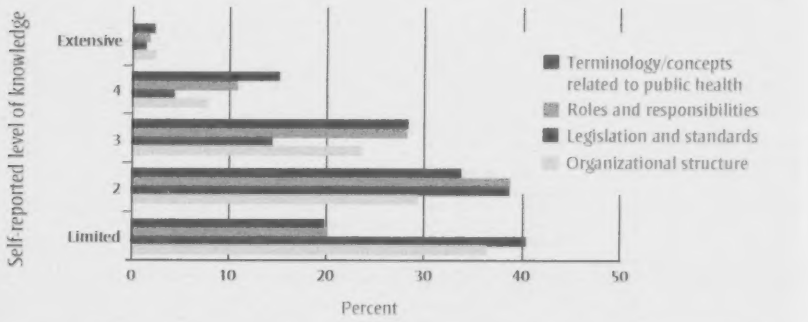


FIGURE 4B
Extent of their knowledge on public health, according to planners (n = 301)



available from: http://www.opha.on.ca/What-We-Do/Projects/Built-Environment.aspx

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Conflict of interest

We do not have any conflicts of interest to disclose.

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For more information

The Ontario Professional Planners Institute provides leadership in achieving healthy and sustainable communities in Ontario through the Institute's Calls to Action and Policy Papers. These are available here:

http://ontarioplanners.ca/Policy/Healthy-Communities-bull-Sustainable-Communities

Public Health Agency of Canada. Crossing sectors: experiences in intersectoral action, public policy and health [Internet]. Ottawa (ON): Public Health Agency of Canada; 2007. Available from: http://www.phac-aspc.gc.ca/publicat/2007/cro-sec/index-eng.php

At-a-glance

Emergency department surveillance of thermal burns and scalds, electronic Canadian Hospitals Injury Reporting and Prevention Program, 2013

Jennifer Crain, MA (1); Steven McFaull, MSc (1); Deepa P. Rao, PhD (1); Minh T. Do, PhD (1,2); Wendy Thompson, MSc (1)

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Introduction

Although fatality and hospitalization rates for burns in Canada have declined over time,[1,2] less serious cases still commonly present to the emergency department (ED).

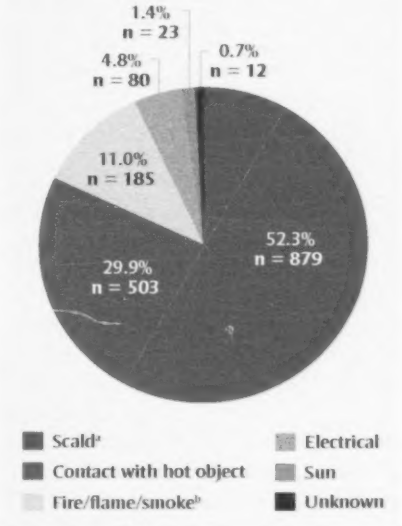
Methods

The Canadian Hospitals Injury Reporting and Prevention Program (CHIRPP) is an injury and poisoning surveillance system administered by the Public Health Agency of Canada, operating in emergency departments of 17 hospitals.[3] We searched the electronic CHIRPP (eCHIRPP) database for ED visits by people of all ages for thermal burns and scalds sustained in 2013. Burns from friction, chemical/caustic agents, and direct contact with lightning were excluded because they present unique circumstances.

Results

Overall, 1682 cases were identified, representing 1.2% (1682/137 245; 1226/100 000 eCHIRPP cases) of injuries reported in 2013. Half were scalds (52.3%; 879/1682) and 29.9% (503/1682) were contact burns from hot objects (Figure 1). The two leading direct causes of scalds were hot beverages at 34.1% (292/856; n = 23 missing) and hot water (not from the tap) at 28.9% (247/856; n = 23 missing). The two leading direct causes of contact burns were stoves/ovens (22.0%; 109/495; n = 8 missing), and fireplaces/accessories (19.6%; 97/495; n = 8 missing). Overall, 13.0% of cases (218/1682) were serious enough to require hospital admission; the highest proportion of hospitalizations was among those exposed to fire/flame/smoke, at 38.9% (72/185).

FIGURE 1
Distribution of burn injuries by mechanism, frequency and percent, all ages, eCHIRPP 2013



Abbreviation: eCHIRPP, electronic Canadian Hospitals Injury Reporting and Prevention Program.

[a] Includes contact with hot water, steam, food, oil, grease, liquid glue and liquid wax.

[b] Includes explosions and contact with hot coals.

While the overall proportion of burns was highest among females, males comprised a higher proportion of burns from all mechanisms except scalds (Table 1). Figures 2 and 3 show age and sex distributions among scalds and contact burns, respectively. Young children were the most prominent age group for both types of burn.

Among burns from fire/flame/smoke, the highest proportion based on age and sex was within males aged 50 to 64 years (n = 16; 782/100 000 eCHIRPP cases), whereas the highest count was among males aged 15 to 19 years (n = 21; 209.1/100 000

TABLE 1
Distribution of burns by mechanism and sex, proportion per 100 000 records,[a] eCHIRPP 2013

Thermal mechanism	Males	Females
Scald	544.7	767.4
Hot object	393.5	331.3
Fire/flame/smoke[b]	169.2	89.6
Electrical	71.8	40.6
Sun	20.5	11.8
Unknown	7.7	10.1
Total	1207.4	1250.8

Abbreviation: eCHIRPP, electronic Canadian Hospitals Injury Reporting and Prevention Program.

[a] Per 100 000 eCHIRPP cases of all injury types among the same sex.

[b] Includes explosions and contact with hot coals.

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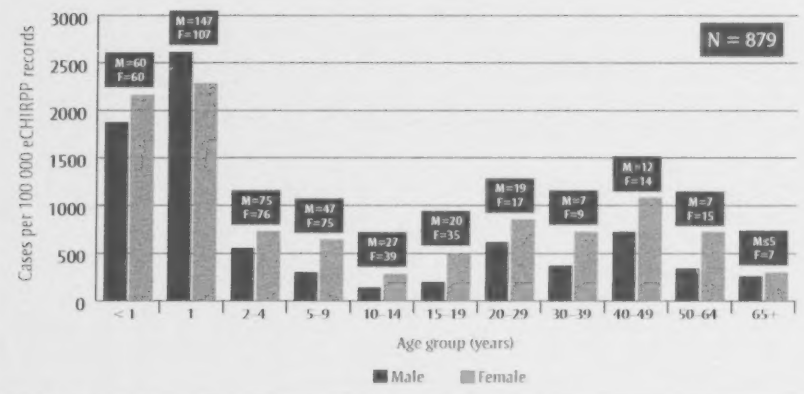
FIGURE 2
Distribution of scalds[a] by age group and sex, frequency and proportion per 100 000[b] records, eCHIRPP 2013



Abbreviation: eCHIRPP, electronic Canadian Hospitals Injury Reporting and Prevention Program; F, females; M, males.

Note: The coloured bars represent the proportion of males/females involved in scaldings per 100 000 eCHIRPP injuries of all types.

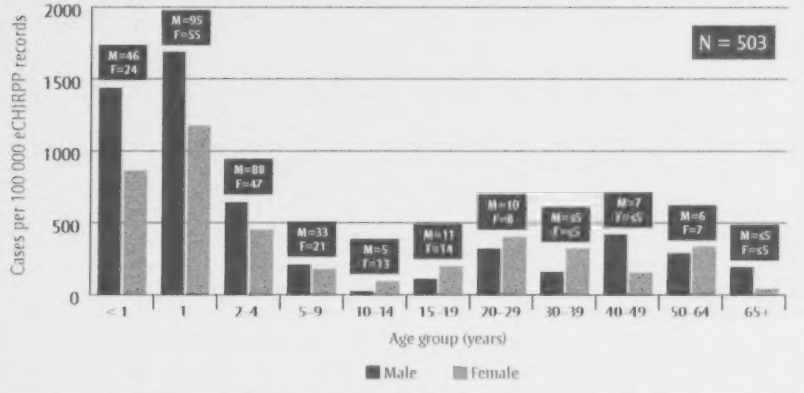
[a] Includes contact with hot water, steam, food, oil, grease, liquid glue or liquid wax.

[b] Per 100 000 eCHIRPP cases of all injury types within the specified age group and sex.

eCHIRPP cases). The highest proportion of burns from fire/flame/smoke among females occurred among those aged 20 to 29 years (n = 6; 302.3/100 000 eCHIRPP cases).

Males and females aged 20 to 29 years shared the highest proportions of sun burns (64.8 and 151.1/100 000 eCHIRPP cases, respectively). The proportion of electrical burns was highest among males aged under one year (n = 7; 219.0/100 000 eCHIRPP cases), whereas the highest count was among males aged 2 to 4 years, at 13 cases. Among adults with electrical burns, the proportion was highest among males aged 20 to 29 years (n = 5; 162.0/100 000 eCHIRPP cases).

FIGURE 3
Distribution of burns from contact with hot objects, by age group and sex, frequency and proportion per 100 000[a] records, eCHIRPP 2013



Abbreviations: eCHIRPP, electronic Canadian Hospitals Injury Reporting and Prevention Program; F, females; M, males.

Note: The coloured bars represent the proportion of males/females involved in scaldings per 100 000 eCHIRPP injuries of all types.

[a] Per 100 000 eCHIRPP cases of all injury types within the specified age group and sex.

Discussion

Burns appear consistently in the CHIRPP. The high proportion of scalds and contact burns to young children points to social and biological risk factors, including more time spent at home (where most burns occur), and younger, thinner skin that is more prone to burning. Improved awareness of these risk factors and appropriate safety measures is recommended.

Limitations

The results for less common burn mechanisms may be subject to random variation due to small sample sizes. The cases described also do not represent all thermal burns and scalds in Canada, as only some hospitals participate in the CHIRPP. Along with older teens and adults, Aboriginal persons and rural inhabitants are underrepresented because most CHIRPP sites are pediatric hospitals in major cities. Fatalities are also underrepresented because emergency department data do not capture people who died before being taken to hospital or after being admitted.

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Letter to the Editor

Who benefits from the professionalization of health promotion?

Tweet this article

To the editor:

In 2007, Health Promotion Ontario (HPO) began working to advance the "profession" of health promotion (HP) in Canada through development of national competencies for health promoters. Their work was continued by the Pan-Canadian Network for Health Promoter Competencies[1] ("the Network"). Funded by the Public Health Agency of Canada, the Network aimed to address (1) the recommendation made by the Canadian Joint Task Group on Public Health Human Resources[2] for function-specific competencies (including "HP Specialists"); and (2) the marginalization health promoters face in practice. The current health promoter competencies were released in November 2015,[1] following a series of literature reviews and practitioner consultations.

This is admirable work, done by passionate, knowledgeable individuals. I echo their desire to advance HP in Canada and that greater appreciation for health promoters is warranted. However, their conceptualization of HP as a profession will hinder the integration of HP approaches across all areas of public health. This is a lesson we must learn from similar efforts in the UK. Recounting the evolution of HP in the United Kingdom, Orme and colleagues[3] report that at one point "health promotion was essentially torn between following a narrow professionalization agenda, thereby becoming less effective, or pursuing its goal of developing effective partnerships and practices, thereby losing its professional status."[3,p.417] HP in Canada may be at a similar crossroads.

McQueen and Kickbusch report HP "has long sought to define itself, and this has been an admirable, if futile, pursuit."[4,p.1] As the "new kid on the block," it is understandable that health promoters desire professionalization given that established (and mostly regulated) professions comprise the bulk of the public health workforce. In fact, HPO includes the term "profession" in their citation of the World Health Organization's definition of HP (even though the word is absent from the actual definition).[5] From reviewing the available materials that have informed the Network's activities, I am concerned that the professionalization of HP is occurring without thoughtful consideration of potential unintended negative consequences—namely, that the more HP is professionalized, the less it will be integrated across all areas of public health practice. If the professionalization of HP advances, I predict it will benefit a small group of health promoters at the expense of many.

Health promoters, their public health colleagues and the Canadian public are best served by improving the HP aspects of the Core Competencies for Public Health in Canada. We need to broaden these competencies for all, not create distinct ones for health promoters. "Health promotion is not a new and separate discipline, but a necessary and timely reconsideration of public health."[6,p.3]

Sincerely,

J. Ross Graham, MSc, CHE

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Other PHAC publications

Researchers from the Public Health Agency of Canada also contribute to work published in other journals. Look for the following articles published in 2016:

Austin SE, Biesbroek R, Berrang-Ford L, Ford JD, **Parker S**, **Fleury MD**. Public health adaptation to climate change in OECD countries. Int J Environ Res Public Health. 2016;13(9):889. doi: 10.3390/ijerph13090889.

Brazeau S, **Kotchi SO**, **Ludwig A**, **Turgeon P**, **Pelcat Y**, Aube G, **Ogden NH**. Tele-epidemiology and public health in the Canadian context. European Space Agency (Special Publication). 2016.

Delnord M, Hindori-Mohangoo AD, Smith LK, Szamotulska K, Richards JL, **Deb-Rinker P**, **Rouleau J**, et al. Variations in very preterm births rates in 30 high-income countries: are valid international comparisons possible using routine data? BJOG Int J Obstet Gynaecol. 2016. doi: 10.1111/1471-0528.14273.

Kotchi SO, **Brazeau S**, **Ludwig A**, Aube G, **Berthiaume P**. Earth observation and indicators pertaining to determinants of health-an approach to support local scale characterization of environmental determinants of vector-borne diseases. European Space Agency (Special Publication). 2016.

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Metcalfe A, Mathai M, **Liu S**, **Leon JA**, Joseph KS. Proportion of neonatal readmission attributed to length of stay for childbirth: a population-based cohort study. BMJ Open. 2016;6(9). doi: 10.1136/bmjopen-2016-012007.